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ANTIMICROBIAL ACTIVITY OF NATURAL COMPOUNDS FROM SPONGE – DERIVED FUNGUS *ASPERGILLUS FLOCCULOSUS* 01NT.1.1.5

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SUMMARY

The *Aspergillus* fungi have been an important source of natural products that are useful for exploration in medicine, agriculture and industry. In our continuous investigation to search for new antimicrobial agents from marine-derived fungi, one new phomaligol A2 (**1**), together with three known compounds, wasabidienone E (**2**), aspertetranone D (**3**) and mactanamide (**4**), were obtained from the EtOAc extract of the culture medium of the marine-derived fungus *Aspergillus flocculosus* (*A. flocculosus*) 01NT.1.1.5 isolated from the sponge *Stylissa* sp. at Nhatrang Bay, Vietnam. Their chemical structures were elucidated by analysis of 1D and 2D NMR and mass spectroscopic data, as well as by comparison of the corresponding data to those previously reported in the literature. Furthermore, the aim of this study was also to evaluate the antimicrobial activity of these compounds against pathogenic microbes including *Escherichia coli* (*E. coli*) ATCC 25922, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853, *Staphylococcus aureus* (*S. aureus*) ATCC 25923, *Bacillus cereus* (*B. cereus*) ATCC 11778, *Streptococcus faecalis* (*S. faecalis*) ATCC 19433, *Listeria monocytogenes* (*L. monocytogenes*) ATCC 19111, and *Candida albicans* (*C. albicans*) ATCC 10231. Among the compounds, **1**-**3** were inhibitory on the growth of the yeast *C. albicans* with minimum inhibitory concentration (MIC) value of 16 µg/mL, which was more potent than amoxicillin and cefotaxime (MIC > 256 µg/mL), antimicrobial drugs as positive references. Moreover, compounds **1**-**4** were also found to be active against other pathogens including *P. aeruginosa* and *S. faecalis* with MIC values of 16 µg/mL and 32 µg/mL, respectively. Compound **4** had no inhibitory activity against *L. monocytogenes*, whereas compounds **1**-**3** had ability to against this strain with MICs of 32 to 64 µg/mL. Four of tested compounds exhibited antibacterial activity against *B. cereus* and *E. coli* with MIC values of 64-128 µg/mL. This is the first report about these compounds with antimicrobial activity obtained from marine fungus *A. flocculosus* isolated in Vietnam.

Keywords*:* *Aspergillus flocculosus*, antimicrobial activity, aspertetranone D, mactanamide, phomaligol A2, wasabidienone E.

INTRODUCTION

Nowadays, in spite of the advance in human drugs, infectious diseases related to the emergence of pathogens, are still major issues in public healthy worldwide, especially in developing countries. The widespread of antimicrobial resistance microbes has been reported over the world that demands more effective antimicrobial compounds. Despite the impressive advance in producing antimicrobial substances by chemical and bio-engineered synthesis, nature particularly marine environment has still considered as the richest source for new antimicrobial compounds (Blunt *et al*., 2010). Novel antimicrobial compounds from marine microbes have been increasingly discovered in recent years (Du *et al.*, 2014; Habbu *et al.*, 2016; Handayani *et al.*, 2015). So far, a great number of antimicrobial compounds have been found in a handful of the one million different microbial species (Brown *et al.*, 2014).

Natural metabolites from marine fungi are considered an important source for novel

antimicrobial compounds because of their abundant fungal species diversity, their rich secondary metabolites and the improvements in their genetic breeding and fermentation processes (Li *et al.*, 2014; Du *et al.*, 2014).

The *Aspergillus* genus has more than one hundred species, and belongs to the Ascomycota division, Deuteromycotina subdivision, Hyphomycetes class, Moniliales order, Moniliaceae family. The species are widely found in nature and diverse in marine ecosystems, are well known for producing antimicrobial and anticancer compounds, bio- surfactants, *etc.* (Li, 2010). Thus, the *Aspergillus* fungi have been an important source of natural products useful for exploration in medicine, agriculture and industry (Petersen *et al.*, 2015).

As part of a continuing study to evaluate the drug potential of marine-derived fungi from Vietnam, we isolated and screened 100 fungal strains from various marine habitats at Nhatrang Bay for antimicrobial activity. Among them, the strain *Aspergillus flocculosus* (*A. flocculosus*) 01NT.1.1.5 was isolated from the sponge *Stylissa* sp. exhibited high activity against tested pathogens (Trinh *et al.*, 2018). Therefore, the strain was analyzed further for causative secondary metabolites. As a result, one new phomaligol A2 (**1**), together with three known compounds, wasabidienone E (**2**) (Soga *et al.*, 1987), aspertetranone (**3**) (Wang *et al.*, 2015) and mactanamide (**4**) (Lorenz *et al.*, 1998) were isolated and identified from this fungus. Furthermore, the isolated compounds were examined for antimicrobial activity. Details of the isolation, structure elucidation, and antibiotic activity of compounds **1**–**4** are presented here.

MATERIALS AND METHODS

General experimental procedures

1D and 2D spectroscopic data were recorded on a Varian Unity 500 NMR spectrometer (MCKinley, Sparta, NJ). ESI-MS data were obtained on a Shimadzu hybrid ion-trap time-of-flight mass spectrometer (Shimadzu, Kyoto, Japan). HPLC was conducted on a column 250 mm x 10 mm i.d., S-5 µm, 12 nm, YMC-Pack-ODS-A, with a PrimeLine Binary pump with RI-101 Shodex, RI detector (Shoko Scientific Co., Yokohama, Japan).

Fungal material

The fungus *A. flocculosus* 01NT.1.1.5 was originally isolated from the sponge *Stylissa* sp. at Nhatrang Bay, Vietnam, in February 2016. The fungus was identified according to its gene sequence of 28S rDNA (GenBank accession number MG972941.1). A BLAST search results indicated that the sequence was similar 100% to the sequence of *A. flocculosus* NRRL 5224. The strain was named as *A. flocculosus* 01NT.1.1.5 and currently preserved in the Marine Microorganism Collection, Nhatrang Institute of Technology Research and Application (NITRA).

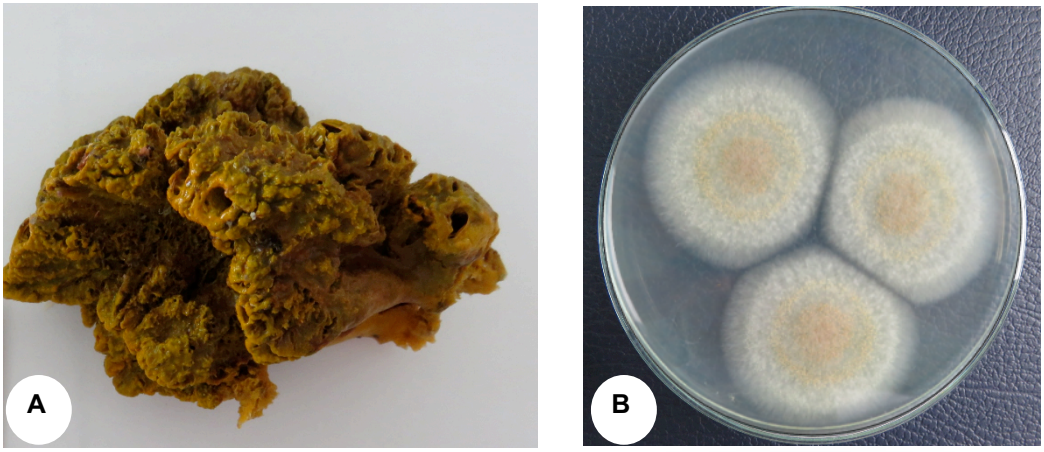


Figure 1. Sponge *Stylissa* sp. (A) and fungus *A. flocculosus* 01NT.1.1.5 (B).

Fermentation, extraction and isolation

The fungal strain was grown stationary at 28°C for 20 days in 45 Erlenmeyer flasks (500 mL), each flask containing 20 g of rice, 20 mg of yeast extract, 10 mg of KH_2PO_4, and 40 mL of natural seawater (Sobolevskaya *et al.*, 2016).

At the end of the incubation period, mycelia and media were homogenized and extracted with EtOAc. The extract of the fungus was concentrated to dry using rotary evaporators at 40°C. The residual suspension (10 g) obtained from the culture of the fungal strain was subjected to ODS open column (200 mm x 50 mm i.d., C18) chromatography followed by stepwise gradient elution with MeOH in H_2O (v/v) (20%, 40%, 60%, 80%, 100%, 2 L each) as the eluent.

The fraction eluted with MeOH in H_2O 40%-1 was utilized to purify compounds by analytical ODS HPLC (column YMC-Pack-ODS-A, 250 mm x 10 mm i.d., 5 µm, flow rate 3 mL/min; RI detector) using isocratic program with 15% ACN in H_2O to yield compounds **1** (9.7 mg) and **2** (45.9 mg).

The fraction eluted with MeOH in H_2O 40%-3 was further purified by a preparative HPLC (column YMC-Pack-ODS-A, 250 mm x 10 mm i.d., 5 µm, flow rate 3 mL/min; RI detector) using isocratic program with 22% ACN in H_2O to yield compounds **3** (30.8 mg) and **4** (4.9 mg).

New phomaligol A2 (1): Yellow brown oil. ESI-MS *m/z* 300.88 $[M + H]^+$, calcd. for $C_{14}H_{20}O_7$. The ^1H and ^{13}C-NMR (CD_3OD) was presented in Table 1.

Wasabidienone E (2): Yellow oil. ESI-MS *m/z* 312.02 $[M + H]^+$, calcd. for $C_{16}H_{25}O_5N$.

^1H-NMR (500 MHz, CD_3OD) δ_H, J (Hz): 5.29 (1H, *s*, H-4), 2.50 (1H, *m*, H-8), 1.45, 1.72 (2H, *m*, H-9), 3.26 (2H, *t*, *J* = 8.5 Hz, H-10), 3.67 (2H, H-11), 1.52 (3H, *s*, 2-Me), 3.94 (3H, *s*, 3-MeO), 1.69 (3H, *s*, 6-Me), 1.18 (3H, *d*, *J* = 10 Hz, 8-Me), 0.93 (3H, *t*, *J* = 15 Hz, 9-Me); ^{13}C-NMR (125 MHz, CD_3OD) δ_C: 192.4 (C-1), 99.9 (C-2), 174.8 (C-3), 78.6 (C-4), 164.0 (C-5), 78.1 (C-6), 175.1 (C-7), 40.1 (C-8), 26.0 (C-9), 44.4 (C-10), 58.8 (C-11), 26.8 (2-Me), 55.2 (3-MeO), 5.9 (6-Me), 15.5 (8-Me), 10.5 (9-Me). These spectroscopic data were suitable with the ones in the literature (Soga *et al.*, 1987).

Aspertetranone D (3): Cream solid. ESI-MS *m/z* 435.11 $[M - H]^-$, calcd. for $C_{22}H_{28}O_9$.

^1H-NMR (500 MHz, CD_3OD) δ_H, J (Hz): 4.34 (1H, *s*, H-6), 2.72, 2.80 (2H, *d*, *J* = 17, 18 Hz, H-10), 2.04 (1H, *m*, H-11), 2.34 (1H, *dd*, *J* = 9, 9.5 Hz, H-11a), 4.58 (1H, *d*, *J* = 9 Hz, H-12), 2.25 (3H, *s*, 3-Me), 1.94 (3H, *s*, 4-Me), 1.40 (3H, *s*, 5a-Me), 1.33 (3H, *s*, 8-Meα), 1.37 (3H, *s*, 8-Meβ), 1.25 (3H, *d*, *J* = 7, 11-Me); ^{13}C-NMR (125 MHz, CD_3OD) δ_C: 164.5 (C-1), 157.7 (C-3), 107.7 (C-4), 163.6 (C-4a), 84.1 (C-5a), 73.3 (C-6), 75.5 (C-6a), 208.3 (C-7), 54.9 (C-8), 211.1 (C-9), 45.2 (C-10), 75.4 (C-10a), 39.2 (C-11), 39.8 (C-11a), 63.2 (C-12), 101.9 (C-12a), 15.8 (3-Me), 8.0 (4-Me), 16.8 (5a-Me), 24.4 (8-Meα), 22.6 (8-Meβ), 9.9 (11-Me). These spectroscopic data were suitable with the ones in the literature (Wang *et al.*, 2015).

Mactanamide (4): White powder. ESI-MS *m/z* 339.05 $[M - H]^-$, calcd. for $C_{19}H_{20}O_4N_2$.

^1H-NMR (500 MHz, CD_3OD) δ_H, J (Hz): 2.84 (1H, *dd*, *J* = 11.5, 3.5 Hz, H-3), 4.21 (1H, *m*, H-6), 2.77, 3.11 (2H, *dd*, *J* = 7,5; 13,5/3,5; 13,5 Hz, H-7), 6.30 (1H, *d*, *J* = 7,5 Hz, H-10), 6.88 (1H, *t*, H-11), 6.30 (1H, *d*, H-12), 3.15, 3.18 (2H, *dd*, H-14), 7.26 (1H, *br m*, H-16), 7.12 (1H, *br m*, H-17), 7.25 (1H, *br m*, H-18), 7.12 (1H, *br m*, H-19), 7.26 (1H, *br m*, H-20), 3.02 (3H, *s*, H-21); ^{13}C-NMR (125 MHz, CD_3OD) δ_C: 168.6 (C-1), 53.7 (C-3), 168.6 (C-4), 63.9 (C-6), 24.4 (C-7), 109.5 (C-8), 156.3 (C-9), 106.7 (C-10), 127.9 (C-11), 106.7 (C-12), 156.3 (C-13), 35.8 (C-14), 134.8 (C-15), 128.3 (C-16), 129.5 (C-17), 127.4 (C-18), 129.5 (C-19), 128.3 (C-20), 32.1 (C-21). These spectroscopic data were suitable for the ones in the literature (Lorenz *et al.*, 1998).

Antibacterial assay

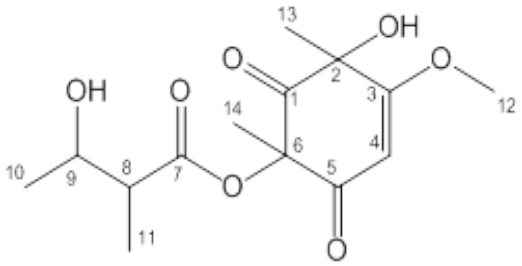
The minimum inhibitory concentrations (MICs) of active compounds against seven pathogens were determined by a dilution method (CLSI, 2016). First, 100 µL of Mueller Hinton Broth medium (MHB) was dispensed into all wells of a microtitre plate. Two-fold dilutions of the compounds in the range of 256-0.125 µg/mL were prepared in the plates. Amoxicillin and cefotaxime were used as positive controls. The turbidity of the microbial suspensions was measured at 600 nm wavelength, and adjusted to match the 0.5 McFarland standard (10^8 colony forming units/mL). Subsequently, 5 µL of bacterial culture was dispensed into each well 96-well plates. Finally, the plates were incubated at 37°C for 18-36 hours, and the MIC values were inspected as the lowest concentrations in which no growth could be observed. Antimicrobial assay was performed at least triplicate.

RESULTS AND DISCUSSION

The fungus was cultured for 20 days on rice medium. The EtOAc extract of the culture was purified by a combination of C18 gel column chromatography and reversed-phase HPLC to yield four individual compounds including one new phomaligol A2 (**1**), together with three known compounds, wasabidienone E (**2**), aspertetranone D (**3**) and mactanamide (**4**).

Compound **1** was obtained as a yellow brown oil. The ESI-MS spectrum showed a quasimolecular ion peak at *m/z* 300.88 $[M+H]^+$, corresponding to the molecular formula of $C_{14}H_{20}O_7$.

The ^{1}H NMR spectrum of **1** (Table 1) exhibited signals for two methyl groups of cyclohexen ring (δ_H 1.55/H-13; 1.66/H-14), a methoxyl group (δ_H 3.89/H-12), and an aromatic proton (δ_H 5.62/H-4). Two olefinic carbons (δ_C 173.7/C-3 and 99.2/C-4), three ketone carbons (δ_C 202.2/C-1, 192.6/C-5 and 175.6/C-7), two oxygenated carbons (δ_C 72.7/C-2 and 82.2/C-6), and a methoxy carbon (δ_C 56.3/C-12) were observed in the ^{13}C NMR data of **1** (Table 1). The ^{1}H NMR spectrum of **1** also showed additional signals of two methyl groups (δ_H 1.22/H-10 and 1.23/ H-11), two methine protons (δ_H 2.46/H-8 and 3.84/H-9). The remaining six carbon signals were attributed to a sec-butyl (δ_C 20.2/C-10, 12.1/C-11, 68.4/C-9, and 46.5/C-8) and two methyl groups (δ_C 22.7/C-14, 20.7/C-13).



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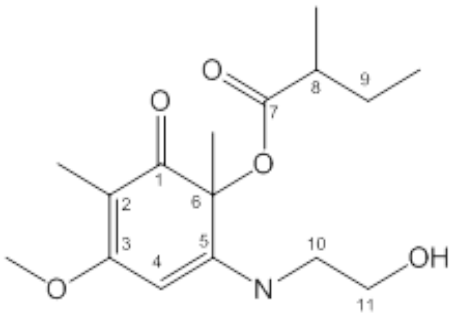
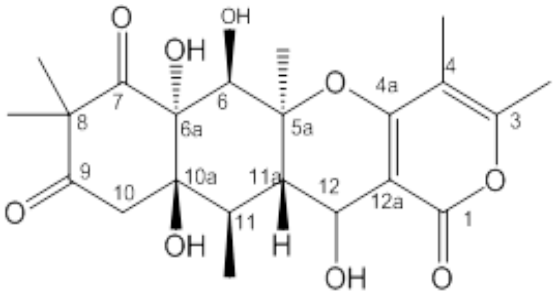
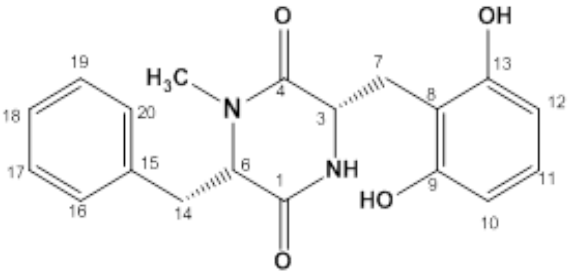


Wasabidienone E (**2**)



Aspertetranone D (**3**)



Mactanamide (**4**)

Figure 2. Structures of compounds **1** - **4**.

The COSY spectrum showed coupling between terminal methyl protons (δ_H 1.22/ H-10) and methine proton (δ_H 3.84/H-9) which were coupled with a methine proton at δ_H 2.46 (H-8), which in turn coupled with a secondary methyl group (δ_H 1.23/H-11) (Figure 3).

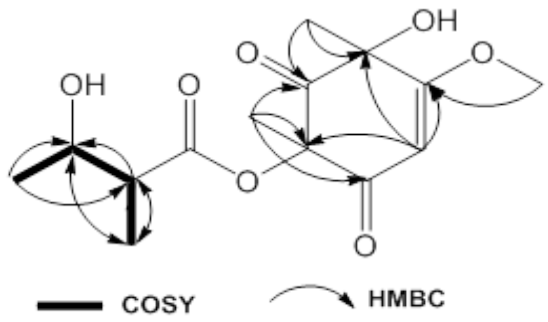


Figure 3. Key COSY and HMBC correlations of **1**.

In the HMBC spectrum, correlations were observed from the methyl protons H-10 (δ_H 1.22) and H-11 (δ_H 1.23) to carbons C-8 (δ_C 46.5) and at C-9 (δ_C 68.4). Furthermore, HMBC correlations from H_3-13 (δ_H 1.55) to C-1 (δ_C 201.1) and C-2 (δ_C 72.7), from H_3-14 (δ_H 1.66) to C-1 (δ_C 201.1), C-5 (δ_C 192.6) and C-6 (δ_C 82.2), and from H_3-12 (δ_H 3.89) to C-3 (δ_C 173.7). Methine protons at δ_H 2.46 (H-8) showed HMBC correlations to the carbonyl carbon at δ_C 68.4 (C-9) and δ_C 12.1 (C-11). Methine protons at δ_H 3.84 (H-9) had HMBC correlations with C-11 (δ_C 12.1). Besides, HMBC spectrum also indicated the correlations from an aromatic proton H-4 (δ_H 5.62) to carbons C-2 (δ_C 72.7), C-3 (δ_C 173.7), C-5 (δ_C 192.6) and C-6 (δ_C 82.2) (Figure 3).

Table 1. NMR data of compound **1**.

Pos.	**1**		**Phomaligol A (**Elbandy *et al.*, 2009)	
	δ_H, *J* (Hz)	δ_C	δ_H, *J* (Hz)	δ_C
1		201.1		202.5
2		72.7		73.5
3		173.7		173.0
4	5.62 (1H, *s*)	99.2	5.56 (1H, *s*)	99.9
5		192.6		191.7
6		82.2		81.1
7		175.6		175.8
8	2.46 (1H, *m*)	46.5	2.50 (1H, *m*)	39.8
9	3.84 (1H, *m*)	68.4	1.73 (1H, *m*)	26.6
10	1.22 (3H, *d*, 6 Hz)	20.2	0.96 (3H, *t,* 7.5 Hz)	11.3
11	1.23 (3H, *d*, 7 Hz)	12.1	1.17 (3H, *d*, 7 Hz)	16.1
12	3.89 (3H, *s*)	56.3	3.87 (3H, *s*)	56.8
13	1.55 (3H, *s*)	20.7	1.65 (3H, *s*)	24.1
14	1.66 (3H, *s*)	22.7	1.70 (3H, *s*)	23.4
2-OH	3.65 (1H, *s*)		2.80 (1H, *br s*)	
9-OH	3.58 (1H, *s*)			

The ^{1}H and ^{13}C NMR spectrum of **1** were nearly similar to that of phomaligol A, isolated from the sponge-derived fungus *Paecilomyces lilacinus*, except for the additional hydroxyl group located at C-9 (δ_H 3.58/OH-9, δ_C 68.4/C-9) (Elbandy *et al.*, 2009). Thus, the compound **1** was assigned as a new compound and named phomaligol A2.

Compounds **1**–**4** showed antimicrobial activity on *E. coli*, *P. aeruginosa*, *S. aureus, B. cereus*, *S. faecalis*, *L. monocytogenes*, and *C. albicans* with various values of minimum inhibitory concentration (MIC) (Table 2). Among these compounds, **1**-**3** exhibited antibiotic activities towards *C. albicans* with MIC of 16 µg/mL, whereas compound **4** showed antifungal activity against *C. albicans* with the MIC of 32 µg/mL. Similar report on the compound mactanamide isolated from marine-derived fungus *Aspergillus* sp., also demonstrated antibiotic activity towards *C. albicans* (Lorenz *et al.*, 1998).

Table 2. Minimum inhibitory concentration (MIC, µg/mL) of compounds **1**–**4** against seven pathogens.

Compounds	*E. coli*	*P. aeruginosa*	*S. aureus*	*L. monocytogenes*	*B. cereus*	*S. faecalis*	*C. albicans*
1	64	16	128	32	128	32	16
2	64	16	64	64	128	32	16
3	64	16	64	32	64	32	16
4	128	16	64	> 256	64	32	32
Amoxcillin	8	128	0.25	0.25	> 256	> 256	256
Cefotaxime	0.25	4	0.5	64	64	4	> 256

Note: Amoxcillin and cefotaxime were positive drugs.

Compounds **1**-**4** also demonstrated prominent antibacterial activity against *P. aeruginosa* (MIC 16 µg/mL), which were higher than that of the positive control amoxicillin (with MIC value of 128 µg/mL). Compound **4** did not illustrate antibacterial activity against *L. monocytogenes*. In conclusion, sponge-derived fungus *A. flocculosus* 01NT.1.1.5 might produce antibacterial secondary metabolites towards different microbes. It is believed that searching for natural products synthesized by marine fungi could be a promising way to combat the emerging of pathogens.

CONCLUSION

From the ethyl acetate extract of culture medium of a fungus *A. flocculosus* 01NT.1.1.5 isolated from the sponge *Stylissa* sp. at Nhatrang Bay, we obtained one new phomaligol A2 (**1**), together with three known compounds, wasabidienone E (**2**), aspertetranone D (**3**) and mactanamide (**4**). All of these compounds showed antimicrobial activity towards microorganisms with various values of MICs. The results indicated that marine fungus *A. flocculosus* 01NT.1.1.5 could produce natural compounds against pathogens. The remaining fractions and other bioactivities study of these compounds are conducting in advance.

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HOẠT TÍNH KHÁNG SINH CỦA HỢP CHẤT TỰ NHIÊN TỪ CHỦNG *ASPERGILLUS FLOCCULOSUS* 01NT.1.1.5 PHÂN LẬP TỪ BỌT BIỂN

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TÓM TẮT

Các loài vi nấm *Aspergillus* được xem là nguồn quan trọng cho các hợp chất tự nhiên ứng dụng trong y dược, nông nghiệp và công nghiệp. Trong tiến trình nghiên cứu của chúng tôi về các hợp chất kháng sinh mới từ vi nấm biển, một hợp chất mới phomaligol A2 (**1**), cùng với ba hợp chất đã biết wasabidienone E (**2**), aspertetranone D (**3**) và mactanamide (**4**) được thu nhận từ dịch chiết etyl acetate môi trường lên men chủng vi nấm biển *Aspergillus flocculosus* (*A. flocculosus*) 01NT.1.1.5 phân lập từ loài bọt biển *Stylissa* sp. thu ở vịnh Nha Trang, Việt Nam. Cấu trúc hoá học của các hợp chất này được xác định bởi phân tích dữ liệu phổ công hưởng từ hạt nhân 1 chiều, 2 chiều và phổ khối, đồng thời so sánh với các dữ liệu tương ứng với các công trình nghiên cứu trước đây. Bên cạnh đó, nghiên cứu cũng tiến hành đánh giá hoạt tính kháng sinh của các hợp chất thu được đối với các chủng vi sinh gây bệnh bao gồm *Escherichia coli* (*E. coli*) ATCC 25922, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853, *Staphylococcus aureus* (*S. aureus*) ATCC 25923, *Bacillus cereus* (*B. cereus*) ATCC 11778, *Streptococcus faecalis* (*S. faecalis*) ATCC 19433, *Listeria monocytogenes* (*L. monocytogenes*) ATCC 19111, and *Candida albicans* (*C. albicans*) ATCC 10231. Trong số các hợp chất này, hợp chất **1**-**3** ức chế sự tăng trưởng của nấm men *C. albicans* với nồng độ ức chế tối thiểu (MIC) là 16 µg/mL. Hoạt tính của các hợp chất này hiệu quả hơn khi so sánh với amoxicillin và cefotaxime (MIC > 256 µg/mL), thuốc kháng sinh được sử dụng làm đối chứng dương. Bên cạnh đó, các hợp chất **1**-**4** cũng thể hiện hoạt tính kháng các chủng vi khuẩn gây bệnh khác bao gồm *P. aeruginosa* và *S. faecalis* với MIC lần lượt 16 µg/mL và 32 µg/mL. Hợp chất **4** không có hoạt tính ức chế đối với chủng *L. monocytogenes*, trong khi các hợp chất **1**-**3** có khả năng kháng chủng này với MIC từ 32 đến 64 µg/mL. Bốn hợp chất thử nghiệm đều thể hiện hoạt tính kháng khuẩn đối với chủng *B. cereus* và *E. coli* với các giá trị MIC 64-128 µg/mL. Đây là báo cáo đầu tiên về các hợp chất có hoạt tính kháng sinh thu được từ chủng vi nấm biển *A. flocculosus* phân lập tại Việt Nam.

Keywords: *Aspergillus flocculosus, aspertetranone D, hoạt tính kháng sinh, mactanamide, phomaligol A2, wasabidienone E*